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Early-Life Adversity, Systemic Inflammation, and Co-mMorbid Physical and Psychiatric Illnesses of Adult Life

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Abstract

Recently, the evidence of increased immune activation in patients with schizophrenia has suggested a role for the immune system in the development of psychosis. However, what is causing this increased immune activation and how this leads to the development of psychopathology remains still unclear. In this chapter we discuss the evidence about the role of childhood trauma as possible underlying cause of the increased immune activation in patients with schizophrenia. According to pre-clinical and clinical models, early adverse events can disrupt the homeostatic control of immune responses and lead to enduring inflammatory dysregulation at a peripheral and central level. In fact, persisting systemic inflammation may facilitate peripheral tissues damage and breach the blood-brain barrier, leading to microglia activation and to neuroinflammation.

Such chronic immune dysregulation also appear to partially explain the frequent comorbidity between psychosis and metabolic abnormalities, which have previously mainly considered as side effect of antipsychotic treatment.

Overall, this evidence suggests that early stress may contribute to development of schizophrenia spectrum disorders through a modulation of the peripheral and central immune system and support the immune pathways as possible future therapeutic approach for psychosis.

Keywords

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1. Introduction

In recent decades, research on schizophrenia has increasingly focused on the role of the immune system in the development of psychosis. In particular, the evidence of comorbidity between psychosis and metabolic abnormalities, together contributing to a reduced life expectancy, suggests that specific biological factors, such as an immune dysregulation, may link the aetiology of psychosis and physical health problems. A chronic low-grade immune activation has been consistently shown by studies in patients with schizophrenia spectrum disorders. These immune abnormalities have been detected not only in peripheral tissues (such as blood), but also in the brain, and they have been suggested to contribute to the development of other medical comorbidities, including metabolic and cardiovascular disorders (Leonard et al. 2012). However, what is causing this increased immune activation and how this leads to the development of psychopathology remains still unclear. Different causes have been considered, including perinatal infection, disruption of microbiota, and psychosocial stress. In this chapter we are going to first

discuss the evidence about the role of psychosocial stress, and more specifically childhood trauma, as possible underlying cause of the increased immune activation in patients with schizophrenia. In the second part of this chapter, we will analyse the evidence supporting the underlying role of childhood trauma and related immune dysregulation in the link between psychosis and metabolic disorders.

Childhood trauma is defined as harm, potential of harm or threat of a harm resulting from commission or omission by child's caregiver (Sideli et al. 2012). This definition includes a number of adverse experiences, such as physical, sexual and emotional abuse, neglect, parental death and bullying, but the most common forms of trauma, reported by both men and women, are physical abuse, physical neglect, and emotional abuse, all of which are likely to co-occur (Scherrer et al. 2004). Neglect, the failure to provide for all aspects of the child's well-being, is considered the most frequent form with 78.5% of children exposed in the general population; physical abuse is reported in 17.6%, and it is defined as the use of physical force that harms the child's health, survival, development or dignity (Dubowitz et al. 2004). Approximately 8% of males and 20% of females universally experienced childhood sexual abuse (the involvement in sexual activity that a child is unable to give consent to, or is not developmentally prepared for), with the highest prevalence in Africa (34.4%), followed by Asia (in particular China and India), America and Europe, with 23.9%, 10.1%, and 9.2%, respectively (Verdolini et al. 2015). Finally, emotional abuse is the failure to provide children with a supportive environment. Actually, it seems to have higher prevalence than sexual and physical abuse, but it is more difficult to measure and quantify (Holmes and Slap 1998).

2. Association Between Childhood Trauma and Psychosis

Childhood exposure to adverse experiences has been associated with an increased risk of psychosis, mood disorders and other medical disorders in general, like cardiovascular disorders or diabetes (Varese et al. 2012; Coelho et al. 2014). Several studies have outlined the high prevalence of a history of childhood adversities among patients with psychosis. For example, in a comprehensive review in 2005, Read and colleagues reviewed 39 studies on female in- and out-patients with schizophrenia and demonstrated that the majority of female and male patients reported either cChildhood sSexual aAbuse (CSA) or cChildhood pPhysical aAbuse (CPA) (Read et al. 2005). A more recent study by Varese et al. (2012) found that childhood trauma increases the risk of psychosis with an OR of 2.8. Moreover, they showed that if the adversities considered as risk factors were entirely removed from the population, the number of people with psychosis would be reduced by 33%. It has also been showed that, with the exception of parental death, all types of adversities were related to an increased risk of psychosis. This suggests that psychosis risk is increased by the exposure to adverse experiences in general, rather than to a specific type of trauma.

When looking at studies investigating subjects at "ultra-high risk" of developing psychosis, trauma has been repeatedly found to predict transition to psychosis in this population (Mayo et al. 2017). Sexual abuse has been shown to be the most common form of childhood trauma associated with later psychosis conversion, followed by physical abuse (Bechdolf et al. 2005; Conus 2010). Finally, similarly to findings on sexual abuse history, increased severity and duration of individuals' bullying history has also been linked to the emergence of psychotic symptoms (Arseneault et al. 2011).

The most consistent finding about the association between childhood maltreatment and psychosis is that a history of childhood trauma increases specifically positive symptoms. Already in 1994,

Ross and colleagues found that in-patients with schizophrenia with a history of sexual or physical abuse in their childhood had significantly more positive schizophrenia symptoms, especially hallucinations, and slightly fewer negative symptoms than those not abused (Ross et al. 1994). This evidence has been replicated in more recent studies (Ajnakina et al. 2016). Similarly, Bendall et al. (2013) reported that first episode psychosis (FEP) patients exposed to childhood sexual abuse had more severe hallucinations and delusions (Bendall et al. 2013). According to their findings, childhood sexual abuse, especially rape, was associated with auditory verbal hallucinations, whereas victimization (physical abuse and bullying) predicted paranoia as well as auditory verbal hallucinations. Separation experiences (placements in foster care or institutions) were also associated with paranoia.

Trauma has also been suggested to influence the content of hallucinations, with patients experiencing hallucinations with themes similar to their trauma (Hardy et al. 2005). Furthermore, childhood trauma has a negative effect on cognitive functions in healthy individuals as well as in patients with psychosis and their high-risk offspring, in particular in relation to general cognitive abilities, memory, and executive functions. (Aas et al. 2011; Berthelot et al. 2015; Bucker et al. 2012). By contrast, several studies (Read and Ross 2003; Resnick et al. 2003; Lysaker et al. 2001) have found no differences in negative symptoms prevalence between abused and non-abused in-patients, whereas two adult in-patient studies found slightly fewer negative symptoms in abused subjects (McCormick and Goff 1991; Ross et al. 1994; Ajnakina et al. 2016).

3. Childhood Trauma and Immune Activation

Childhood adversities can be considered as environmental insults happening in a critical developmental phase of life. Interestingly, they have been suggested to alter the immune system

function and to finally result in a chronic immune activation. Supporting this hypothesis, childhood adversities are strongly associated with acute and persistent inflammatory dysregulation, namely, increased blood levels of C reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), and such inflammation persists throughout adulthood (Coelho et al. 2014) offering a potential molecular pathway by which early trauma may increase susceptibility to psychiatric disorders (Baumeister et al. 2016). The most supported hypothesis is that early stress causes a pro-inflammatory status that may influence the response to inflammatory challenges during adult life, further contributing to behavioural and cognitive alterations. As a result, childhood adversities may become an important preventable cause of psychiatric disorders, including psychosis.

As far as evidence of peripheral inflammation is concerned, we have recently conducted a meta-analysis of all studies investigating history of childhood maltreatment and inflammatory markers in adulthood (Baumeister et al. 2016). The meta-analysis included studies on both general and clinical populations (with psychiatric and physical disorders) and focused on CRP, IL-6 and TNF-α as these are the most examined inflammatory markers in psychiatric research. Results showed a significant association between childhood trauma and inflammatory markers in adulthood, with greatest effect size for TNF-α (z = 0.20, 95% CI = 0.10–0.29) followed by IL-6 (z = 0.09, 95% CI = 0.04–0.15) and then CRP (z = 0.08, 95% CI = 0.04–0.11). Another important finding from this study was that different types of trauma exposure impacted differentially on the inflammatory markers: physical and sexual abuse was associated with significant increased TNF-α and IL-6, but not CRP. Conversely, CRP was primarily related to parental absence during early development. How different types of trauma may impact different aspects of immune activity remains unknown;

however, it has been suggested that factors such as context, time and duration of stress exposure may interact with individual trauma type in modulating immune response.

3.1. Preclinical Evidence of the Link Between Early Stress and Increased Inflammation

The first evidence of an association between early stress and immune system dysregulation was derived by preclinical studies. After Ader and colleagues found that rats handled before weaning showed slower development of a transplanted tumour (Ader and Friedman 1965), a number of authors started investigating the association between early-life stress and later immune functioning in rodents and non-human primates (Hennessy et al. 2010; Shanks and Lightman 2001). Stress exposure in early life (i.e., across postnatal days 1–20 in rodents) has been re-created in experimental models including neonatal handling, maternal separation, maternal deprivation, nursery rearing, early weaning, and dexamethasone treatment. For example, maternal separation has been associated with an increased stress reactivity. Measures of immune functioning have included pro-inflammatory cytokines in the plasma, antigen-induced immunoproliferation in the spleen, expression levels of pro-inflammatory genes in the brain, and intestinal microflora. Maternal separation in rats has been associated with elevated pro-inflammatory cytokines in the plasma (Reus et al. 2013; Wieck et al. 2013).

In studies with non-human primates, maternal separation led to an increase in macrophage activity (Coe et al. 1988) and long-term up-regulation in pro-inflammatory gene transcription in monocytes (Cole et al. 2012).

3.2. The Emerging Evidence of Neuroinflammation

The second interesting line of evidence coming from preclinical models is the link between early-life stress and markers of immune function in the central nervous system (CNS) (Reus et al. 2013) in adulthood. For example, in adult rats, early maternal separation is associated with greater synaptic levels of the receptor for the pro-inflammatory cytokine interleukin-1 (IL-1) (Viviani et al. 2014), greater number and motility of cortical microglial processes (Takatsuru et al. 2015), and greater microglia activation (Ganguly and Brenhouse 2015; Mondelli et al. 2017). Microglia are myeloid cells which provide the main form of adaptive immune response in the central nervous system (CNS) and play a crucial role in neuroinflammation. Indeed, neuroinflammation may lead to cognitive and behavioural dysfunction and psychopathology. A model of stress-induced central inflammation has already been created in animals by using stressful physical stimuli, such as restraint and foot shock, which could be applied to parent animals to induce maternal or perinatal stress (Mondelli et al. 2017).

The immediate consequences of early-life stress on animals' brain were investigated by Roque and colleagues in 2016 (Roque et al. 2016). The authors analysed the effect of maternal separation on astrocyte and microglial cell morphology in the hippocampus and hypothalamus of male rat pups and found that maternal separation (MS) caused microglia activation and decrease in astrocyte density in both areas. Moreover, compared with controls, MS rats showed increased IL-1β in the hippocampus and increased TNF-α and IL-6 levels in the hypothalamus. Similarly, Diz-Chaves et al. (2012) showed that prenatal stress induces a basal pro-inflammatory status in the hippocampal formation during adulthood that results in an enhanced activation of microglia and astrocytes in response to pro-inflammatory insults. These findings suggest that early stress may contribute to decreased hippocampal neurogenesis and alter the neuroendocrine axis, leading to both psychopathological manifestation and metabolic abnormalities.

3.3. From Animal to Human Models

Pre-clinical evidence has led to a new insight about the link between stress and inflammation in humans. As far as peripheral inflammation is concerned, it is clear that the immune activation resulting from stress is able to protect the body from possible external challenges. Once released, inflammatory mediators are able to coordinate a variety of cell functions that stimulate and enhance immune activation. In particular, IL-1, IL-6, and TNF-α promote the differentiation of lymphocytes called *cytotoxic T cells*, which kill pathogens that are introduced into the body during physical wounding. These cytokines also promote increased vascular permeability and cellular adhesion, which allows immune cells to leave the blood vessels and migrate to tissues (Dhabhar et al. 2012). However, when such immune activation persists chronically, it may damage vessels and peripheral tissues and lead to cardiovascular diseases.

Moreover, the hypothesis that stress may also reach the brain has progressively been investigated in humans. On one hand, stress-induced peripheral inflammation has been showed to affect the brain and to alter neural activity through different pathways: by active transport of cytokines, by involving macrophage-like cells residing in circumventricular organs, or by the release of second messengers, which in turn stimulate local cytokines. These, in turn, can cross the bBlood-b-Brain bBarrier and determine microglia activation (Cattaneo et al. 2015). They influence cell proliferation and survival depending on their inflammatory state (Mondelli et al. 2017). In response to harmful stimuli, microglial cells undergo a number of changes (Walker et al. 2014) including production of pro-inflammatory cytokines and the expression of several cell surface antigens that promote oxidative stress in the brain.

In humans, central inflammation (in terms of microglial activation)~~,~~ can be investigated with p~~P~~ositron e~~E~~mission t~~T~~omography (PET) using radio ligands for the 18-kDa translocator protein (TSPO), that is, a five-membrane domain protein localized mainly in the outer mitochondrial membrane of steroid-~~-~~synthesizing cells, including those in the c~~C~~entral n~~N~~ervous s~~S~~ystem. TSPO is involved in the transport of cholesterol into mitochondria. Peripheral lipopolysaccharide injection, used as immune challenge in primates, has been shown to increase TSPO expression in a uniform manner across the brain. This, in turn, seems to lead to microglial activation and to the expression of histological markers of brain activation in human post-mortem tissue (Mondelli et al. 2017).

4. An Inflammatory Pathway Linking Childhood Trauma and Psychosis?

As a result of the association of early adversities with both elevated inflammation and with psychosis risk, it is not surprising that patients with schizophrenia who have history of childhood trauma tend to show increased levels of some pro-inflammatory markers, including IL-6 and TNF-α (Dennison et al. 2012). In agreement with these findings, we have also previously shown that FEP patients with history of childhood sexual abuse have higher body mass index (BMI) and increased CRP levels in comparison with controls and patients without a history of sexual abuse (Hepgul et al. 2012). In addition, in another study we have also reported that FEP patients with childhood trauma have significantly higher serum levels of TNF-α and monocyte chemo-attractant protein-1 compared with patients without childhood trauma (di Nicola et al. 2013). The biological pathways linking stress to psychosis remain partly unclear, and although peripheral immune activation has been identified as an important link between the two, other biological systems and mechanisms appear to play a role. In particular, the hypothalamic-pituitary-adrenal (HPA) axis and the effects

of neuroinflammation have been both explored in the link between stress and psychosis and offer further understanding behind the presence of an increased peripheral inflammation in psychotic patients with experience of childhood trauma.

4.1. The Allostatic Systems: The Role of the Nervous System and of the Hypothalamic-Pituitary-Adrenal Axis

A suggested mechanism involved in childhood trauma embedding and then leading to chronic inflammation is the association between childhood adversities and enduring changes in the nervous, the endocrine and the immune systems that are highly integrated. Thus, the activation of one of these systems commonly triggers responses in the others (Danese and McEwen 2012).

4.1.1. The Nervous System

A neurobiological network including cerebral areas such as the thalamus, the sensory cortex and the amygdala is involved in detecting environmental threats. In response to psychosocial stressors, such as early adversities, the amygdala triggers firing in the locus coeruleus, which increases alertness and attention to the environment and induces a bodily response through the activation of the sympathetic nervous system (SNS) (the "fight or flight response").

The SNS, in turn, affects the immune system and regulates pro-inflammatory cytokine production by releasing the neurotransmitter norepinephrine into peripheral tissues. In fact, by binding to β-adrenergic and α-adrenergic receptors, norepinephrine regulates the transcription of pro-inflammatory cytokine genes interleukin (IL)-1 and tumor necrosis factor (TNF)-α, leading to systemic immune activation (Danese and McEwen 2012). Then, a chronic or repeated stimulation of the sympathetic nervous system leads to chronically increased levels of inflammation. In the

same time, key anti-inflammatory pathways, such as the *hHypothalamic--pPituitary--aAdrenal* (*HPA*) axis, are progressively down-regulated under stressful conditions.

4.1.2. The Endocrine System: The Hypothalamic--Pituitary--Adrenal Axis

The principal endocrine effectors of the stress response are localized in the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland. Together, these structures are known as the hypothalamic-pituitary-adrenal axis.

Neurons localized in the medial parvocellular subdivision of the PVN secrete corticotropin-releasing factor (CRF), the principle regulator of the HPA axis. Stress (in this case, early adversities) triggers the release of CRF into hypophysial portal vessels that access the anterior pituitary gland. In turn, CRF induces the release of adrenocorticotropic hormone (ACTH) from corticotropic cells into the systemic circulation. Then circulating ACTH targets the adrenal cortex, where it stimulates glucocorticoid synthesis and secretion from the zona fasciculata (Smith and Vale 2006). Glucocorticoids, such as cortisol, exert their activity by binding to glucocorticoid receptors (GR). However, chronic stress can cause persistent elevated basal glucocorticoids levels and impair glucocorticoids ability to exert the negative feedback on the HPA axis itself. Moreover, glucocorticoids exert a natural anti-inflammatory action, binding GR in the body, but chronic stress leads to an impaired GR sensitivity (glucocorticoid resistance) and then to a prolonged/increased immune activation (Miller et al. 1999). Both HPA axis hyperactivity and increased immune activation are present in maltreated children (Danese and McEwen 2012) and persist in adulthood with several detrimental effects. As a consequence, subsequent responses to stressful situations may be abnormal. Second, the elevation of glucocorticoids levels due to glucocorticoid resistance may endanger the hippocampus and make it vulnerable to potential injury as well as stimulate striatal dopamine release that make patients more prone to psychosis (Read et al. 2001). Finally,

this chronic alteration of the endocrine and immune system may progressively promote metabolic abnormalities and explain their common comorbidity with psychotic disorders. In fact, high cortisol levels can increase glucose levels and fat deposition (Dinan et al. 2004); clinical evidence has also shown that stress can lead to an increased intake of high-calories food (Dallman et al. 2005)~~,~~ and precipitate binge eating (Freeman and Gil 2004).

4.2. The Role of Neuroinflammation

Another hypothesi~~z~~s~~s~~ed mechanism linking early trauma to psychosis is neuroinflammation. Preclinical studies suggest that microglia could be an important mediator of the association between psychosocial stress, in particular early stress, and psychiatric disorders, including psychosis. In fact, microglia activation may in turn be associated with impairment of neurogenesis and lead to structural and functional changes in the brain that predispose individuals to mental illnesses. In humans, ten studies have been published that investigated microglial activity using PET brain imaging in patients with psychosis, but results are inconsistent, probably because of the use of different radiotracers and different ways of analysing the data. Indeed, four of these studies found an increase in TSPO binding, one found an increase in medicated patients but not in drug-naive patients, and the other five did not find significant differences between patients and matched controls (Mondelli et al. 2017).

Findings suggesting the presence of neuroinflammation have already led researchers to support the development of new treatments. In particular, drugs that inhibit or reduce microglial activation are being tested in a number of studies (Mondelli et al. 2017). A preclinical study from Giovanoli et al. (2016) have explored whether an early anti-inflammatory intervention with minocycline during peripubertal stress exposure might prevent the subsequent emergence of

adult behavioural pathology (Giovanoli et al. 2016). They used an environmental two-hit model in mice, in which prenatal maternal administration of the viral mimetic poly(I:C) served as the first hit, and exposure to sub-chronic unpredictable stress during peripubertal maturation as the second hit. Using this model, they examined the effectiveness of the tetracycline antibiotic minocycline, a broad-spectrum tetracyclic antibiotic displaying neuroprotective properties, given during stress exposure, to block stress-induced inflammatory responses and to prevent subsequent behavioural abnormalities. They found that combined exposure to prenatal immune activation and peripubertal stress caused significant behavioural dysfunctions, which minocycline treatment during stress exposure was able to prevent. In addition, the same pharmacological intervention blocked hippocampal and prefrontal microglia activation and interleukin-1β expression in offspring exposed to prenatal infection and peripubertal stress. Minocycline has been suggested as a new potential therapy for negative symptoms in clinical studies of patients with schizophrenia. In two clinical trials comparing minocycline versus placebo, both added to the standard care, patients receiving minocycline showed a greater reduction in negative symptoms (Levkovitz et al. 2010; Chaudhry et al. 2012).

4.3. Possible Role of the Interaction of Childhood Trauma with Other Environmental Factors

A number of environmental insults have been associated with a risk of psychosis, including socioeconomic status, cannabis use, and urbanicity. Epidemiological studies have focused their interest on the interaction between childhood adversities and other environmental risk factors in order to provide broader insights into inflammatory trajectories leading to psychosis onset. In particular, there are studies showing that childhood traumatic events are associated with

increased cannabis use in adulthood (Harley et al. 2010; Houston et al. 2011; Konings et al. 2012). Some pre-clinical data demonstrate that Δ^9-THC in adolescent mice triggers immune dysfunctions that last long after the end of abuse, switching the murine immune system to pro-inflammatory status in adulthood.

Such a pro-inflammatory state they may play a key role in the pathogenesis of neuropsychiatric disorders by modulating neurotransmitter and neuropeptide systems (Kronfol and Remick 2000; Muller and Ackenheil 1998) such as central monoamine activity (DeLisi 1992; Zalcman et al. 1994). This may partly explain why the onset of cannabis consumption at an earlier age has been identified by several authors as a factor contributing to poor prognosis in schizophrenia (Veen et al. 2004; Busse et al. 2012). A modulation of microglia function by cannabinoids, both endogenous and synthetic ones, has also been suggested. This dysregulation might cause an alteration in the neuronal architecture or the neurotransmitter flow (Busse et al. 2012; Leweke and Koethe 2008; Bernstein et al. 2009) meaning that cannabinoid action may not be limited to direct changes at the neurotransmitter level; it may alter the "immune atmosphere" of the brain (Skaper et al. 2013).

5. Inflammation and Physical Health

Another interesting aspect of high levels of inflammation is that they are generally associated with physical health comorbidities, in particular cardiovascular diseases, in both the general population and in patients with psychosis (Russell et al. 2015).

This is because the functions of the metabolic and immune system are highly interdependent. An example is the overlapping function of macrophages and adipocytes. In obesity, these two kinds of cells contribute together to the production of inflammatory mediators, which, together with fatty acids, are able to inhibit the downstream signalling of insulin receptors, eventually leading to

insulin resistance (Wellen and Hotamisligil 2005). Consistently, metabolic-related conditions as obesity, type 2 diabetes and insulin –resistance are usually associated with chronic inflammation (Hotamisligil 2006), in particular with high levels of IL-6 and CRP (Capuzzi and Freeman 2007). Inflammation is also involved in all stages of atherothrombosis, the underlying cause of approximately 80% of all sudden cardiac death (SCD). In fact, inflammatory cells such as macrophages and T lymphocytes, eventually contribute to the formation of the atheromatous lesion, which consists of a lipid pool protected by a fibrous cap. Moreover, the activation of these cells leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors, all of which play important roles in atherogenesis and in the development of cardiovascular events (Willerson and Ridker 2004). In patients with psychosis, cardiovascular issues are even more present than in the general population. For example, as early as 1960 a survey in the USA showed that 40% of hospitalized patients with schizophrenia were overweight, in contrast to 20% of the general population (Gordon et al. 1960), and in 2004, a cross-sectional study by Kato and colleagues found that the prevalence of metabolic syndrome in patients with schizophrenia was 63% and that they had threefold greater risk to develop this syndrome than the general population (Kato et al. 2004).

5.1. Inflammation and Metabolic Complications in Psychosis

Metabolic abnormalities and weight gain in patients with psychosis are widely associated to antipsychotic treatment (Allison and Casey 2001; Mondelli et al. 2013). However, studies have shown impaired glucose tolerance, increased visceral fat and increased obesity and hypertension also in drug-naïve patients (Correll et al. 2014), suggesting an impaired metabolism regardless of medication. For instance, some authors found that prevalence of diabetes in schizophrenia exceeds that in the general population well before the widespread use of the new (atypical)

antipsychotic drugs (Dixon et al. 2000). Therefore, impaired glucose metabolism may be associated with schizophrenia rather than be only a side effect of antipsychotic treatment. To this regard, Perry and colleagues have conducted an interesting meta-analysis on pre-diabetic markers in anti-psychotic naïve FEP. They included 12 studies (a total of 1,137 participants), and they found first-episode psychosis to be related to insulin resistance and impaired glucose tolerance (but not fasting plasma glucose) in the absence of medication (Perry et al. 2016).

On the other hand, in diabetic patients, untreated hyperglycaemia has been associated with alterations of mood state and acute psychosis manifestations (Sahoo et al. 2016).

Again, stress and inflammation are possible common pathways explaining the link between psychosis and metabolic abnormalities. In particular, childhood trauma may have a key role in mediating both.

Interestingly, inflammation has already been suggested to link cardiovascular abnormalities and depression. CRP, IL-1, and IL-6 have been associated with atherosclerosis and depression alike, both in healthy subjects and in cardiac patients. Previous studies have suggested both that inflammation increases risk of depression and that depression causes inflammation in patients with cardiovascular disorders (Elderon and Whooley 2013). Thus, although it remains difficult to disentangle whether such inflammatory mediators serve as triggers of both depression and CVD, act on the causal pathway between them, or result from both conditions, at least it is now clear that inflammatory pathways may be the shared biological mechanisms between mental and physical diseases.

5.2. Childhood Trauma and Metabolic Abnormalities

Again, animal models, like those involving non-human primates, have been a useful source of

evidence suggesting that adverse childhood experiences may influence physical health, especially obesity risk.

Kaufman et al. (2007) showed that compared with normally reared monkeys, those exposed to early stress exhibit greater weight, BMI, abdominal circumference, glucagon-like peptide-1 and decreased glucose disposal rates during hyperinsulinaemic-euglycaemic clamps. In their model of early-life stress (variable foraging demand [VFD]), food insecurity is imposed on monkey mothers for 16 weeks beginning when their nursing offspring are 3–5 months of age. VFD resulted in a range of neurobiological abnormalities, including dysregulation of the HPA axis, manifested in abnormal cerebrospinal fluid cortisol and corticotropin-releasing factor levels. These data suggest that early-life stress during a critical period of neurodevelopment can result in the prepubertal emergence of obesity and insulin resistance.

Evidence of the link between early trauma and metabolic abnormalities is also quite clear from more recent human studies. A meta-analysis conducted by Danese and ~~colleagues~~Tan (2014) on 41 studies in humans suggests that childhood maltreatment predicts obesity, independently from the measures and the definitions used and other potential confounding variables. Stressful psychosocial experiences in childhood might thus be conceptualized as potentially modifiable risk factors for obesity. Thus, prevention or effective treatment of severe cases of childhood maltreatment could avoid development of obesity in adulthood. However, it is still unclear if and how the effect of maltreatment on obesity could be modified through intervention.

Li et al. (2017) showed that childhood maltreatment is an independent risk factor for developing pre-diabetes. They recruited 121 participants from the general population, either with (*n* = 69) or without history of childhood maltreatment (*n* = 52). The authors found a 15% higher glucose area

under the OGTT curve in the maltreated group, together with impaired insulin sensitivity. This group also showed higher CRP and TNF-α levels, both positively correlating with severity of childhood trauma (r = 0.21, 0.23, respectively, both $p < 0.05$). These data suggest an important relationship between childhood maltreatment and increased risk for pre-diabetic state due to glucose intolerance and, impaired insulin sensitivity, and beta cell function. Finally, Rich-Edwards et al. (2012) also showed that severe child abuse is a risk factor for early adult cardiovascular disorders, while Suglia et al. (2014) found that women who experienced sexual abuse in early childhood had a higher prevalence of hypertension (prevalence ratio (PR) 1.43 95% CI 1.00, 2.05) compared with women who did not experience such maltreatment.

5.3. Childhood Trauma and Metabolic Abnormalities in Patients with Psychosis

When looking at schizophrenia -spectrum patients, only three studies have addressed the contribution of childhood trauma to cardio-metabolic risk.

In our study by Hepgul et al. (2012), we found that FEP patients with a history of childhood sexual abuse had higher BMI and CRP levels when compared with healthy controls and patients without childhood sexual abuse. CRP has been recently considered a marker of increased risk of diabetes and other metabolic dysfunction (Bassuk et al. 2004), and has also been similarly linked to chronic psychosocial stress (Miller 2008). Another study (Misiak et al. 2015) revealed that a history of childhood adversities, especially sexual and emotional abuse, is associated with higher systolic and diastolic blood pressure as well as greater levels of low-density lipoproteins (LDL) in FEP patients. Moreover, a study by Rajkumar (2015) found an association between childhood trauma and higher BMI and systolic blood pressure in patients with schizophrenia. In particular, physical abuse was

linked to elevated systolic blood pressure, while emotional abuse and neglect in women were linked to being overweight.

Finally, whether psychotropic drugs may play a role in leading to inflammation, by interacting with childhood adversities, is still unclear. The association between antipsychotic medication and an impaired metabolism is well known (Martin Otano et al. 2013), so that treated patients often show and overall altered metabolic-inflammatory status. Given the already mentioned association between sexual abuse and severity of hallucinations and delusions, it could be hypothesized that higher doses of antipsychotics are prescribed to patients with a history of childhood maltreatment. As a consequence, side effects of medication would be another mechanism linking childhood maltreatment and adulthood inflammation. However, studies investigating this hypothesis are currently lacking, so this should be the aim of future works.

6. Conclusion

In conclusion, susceptibility to psychosis is likely to be influenced by personal history of exposure to early traumatic events. In this model, priming adverse events can disrupt the homeostatic control of immune responses leading to enduring inflammatory dysregulation at a peripheral and central level. In particular, persisting systemic low-grade chronic inflammation may facilitate peripheral tissues damage and breach the blood-brain barrier with activation of microglia and development of neuroinflammation. The immune dysregulation also explains the development of multiaxial comorbidity including metabolic abnormalities and cardiovascular disorders, which have previously mainly considered as side effect of antipsychotic treatment (Fig. 1).

Two important considerations should be drawn from this work: first, research in the field of immunopsychiatry may lead to the development of new treatments targeting immune pathways

in future therapeutic approaches to psychosis. Second, it is clear that early stress might be an important factor to early detect, prevent and better manage the development and treatment of schizophrenia spectrum disorders and any related physical comorbidities.

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Fig. 1 Proposed model through which childhood adversities contribute to development of psychosis and comorbid metabolic abnormalities via activation of peripheral and central immune system

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